

1205447

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

August 06, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/532,779
FILING DATE: December 24, 2003

Certified by



Jon W Dudas

Acting Under Secretary of Commerce
for Intellectual Property
and Acting Director of the U.S.
Patent and Trademark Office

BEST AVAILABLE COPY

17607 U.S. PTO
122403

PTO/SB/16 (08-03)
Approved for use through 7/31/2008. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

16018 U.S. PTO
60/532779

122403

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Lab I No.

INVENTOR(S)					
Given Name (first and middle [if any])		Family Name or Surname		Residence (City and either State or Foreign Country)	
Stefano		Turchetta		Roma, Italy	
Pietro		Massardo		Roma, Italy	
Valentina		Aromatario		Roma, Italy	
Additional inventors are being named on the _____ separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
NOVEL POLYMORPHS OF 1-CYCLOPROPYL-7-((S,S))-2,8-DIAZADICYCLO[4.3.0]NON-8-YL)-6-FLUORO-1,4-DIHYDRO-8-METHOXY-4-OXO-3-QUINOLINE CARBOXYLIC ACID HYDROCHLORIDE AND METHODS FOR THE PREPARATION THEREOF					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
<input checked="" type="checkbox"/> Customer Number:		07278			
OR					
<input type="checkbox"/> Firm or Individual Name		Adda C. Gogoris DARBY & DARBY P.C.			
Address		P.O. Box 5257			
City	New York	State	NY	Zip	10150-5257
Country	US	Telephone	(212) 527-7700	Fax	(212) 753-6237
ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/>	Specification Number of Pages	18	<input type="checkbox"/>	CD(s), Number	
<input checked="" type="checkbox"/>	Drawing(s) Number of Sheets	8	<input type="checkbox"/>	Other	
<input checked="" type="checkbox"/>	Application Data Sheet. See 37 CFR 1.76		(specify):		
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT					
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.					FILING FEE AMOUNT (\$) 160.00
<input checked="" type="checkbox"/> A check or money order is enclosed to cover the filing fees.					
<input checked="" type="checkbox"/> The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 04-0100					
<input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached.					
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are:					

[Page 1 of 1]

Respectfully submitted,

Date December 24, 2003

SIGNATURE Adda C. Gogoris
TYPED OR
PRINTED NAME Adda C. Gogoris
TELEPHONE (212) 527-7727

REGISTRATION NO. 29,714
(if appropriate)
Docket Number: 02901/0200758-US0

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

Express Mail Label No.

Dated:

17607
U.S. PTO
122403

PTO/SB/17 (10-03)

Approved for use through 7/31/2008. OMB 0651-0032

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003, Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$)
160.00

Complete if Known

Application Number Not Yet Assigned
Filing Date Concurrently Herewith
First Named Inventor Stefano Turchetta
Examiner Name Not Yet Assigned
Art Unit N/A
Attorney Docket No. 02901/0200758-USO

METHOD OF PAYMENT (check all that apply)

☒ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☐ Deposit Account:

Deposit Account Number
04-0100

Deposit Account Name
Darby & Darby P.C.

The Director is authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☒ Credit any overpayments

☐ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	160.00

SUBTOTAL (1) (\$)
160.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

Total Claims ** = x =
Independent Claims ** = x =
Multiple Dependent =

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1202	18	2202	9	Claims in excess of 20	
1201	88	2201	43	Independent claims in excess of 3	
1203	290	2203	145	Multiple dependent claim, if not paid	
1204	88	2204	43	** Reissue independent claims over original patent	
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent	

SUBTOTAL (2) (\$)
0.00

** or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for <i>ex parte</i> reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1808	180	1808	180	Submission of Information Disclosure Stmt.	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	800	1802	800	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$)
0.00

SUBMITTED BY

Name (Print/Type) Adda C. Gogoris

Registration No. (Attorney/Agent)

29,714

(Complete if applicable)

Telephone (212) 527-7727

Signature

[Signature]

FLIND BERNARD

63,970

Date

December 24, 2003

Express Mail Label No.

Dated: _____

Application No. (if known):

Attorney Docket No.: 02901/0200758-USO

Certificate of Express Mailing Under 37 CFR 1.10

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail, Airbill No. _____ in an envelope addressed to:

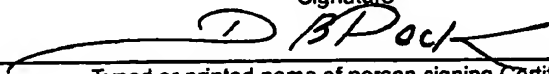
62983950527-US

MS Provisional Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

on December 24, 2003
Date



Signature



Typed or printed name of person signing Certificate

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

Provisional Patent Application Transmittal (1 page)

Fee Transmittal (1 page)

Application Data Sheet (3 pages)

Specification and Claims (18 pages)

Figs. 1-8 (8 sheets)

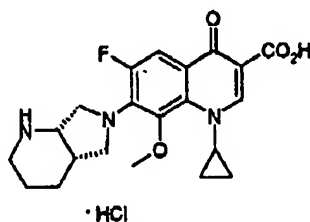
Check No. 3711 in the amount of \$160.00

TITLE

Novel polymorphs of 1-cyclopropyl-7-([S,S])-2,8-diazadicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid hydrochloride and methods for the preparation thereof

ABSTRACT

Two novel crystalline forms, designated form A and form B of the antibacterial agent 1-cyclopropyl-7-([S,S])-2,8-diazadicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid hydrochloride of formula,



the preparation thereof, and their pharmaceutical compositions are described. These crystalline forms, which are characterized by greater stability and ease of preparation and of formulation, can be produced by industrially applicable methods which comprises the steps of:

- a) suspending 1-cyclopropyl-7-([S,S])-2,8-diazadicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid hydrochloride in a solvent selected from an alcohol and a polyalcohol,
- b) heating the mixture under reflux,
- c) cooling,
- d) isolating the product which is separated, (form A) and, additionally,
- e) reslurrying the solid at reflux in a solvent selected from alcohols and polyols or mixtures thereof, in which the resulting mixture has an overall water content of between 2.5% and 0.01% by weight,
- f) isolating the product (form B).

TITLE

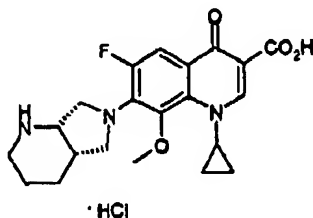
Novel polymorphs of 1-cyclopropyl-7-([S,S])-2,8-diazadicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid hydrochloride and methods for the preparation thereof

Field of the invention

The present invention relates to two novel polymorphs of 1-cyclopropyl-7-([S,S])-2,8-diazadicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid hydrochloride, the methods for the preparation thereof, and pharmaceutical formulations which include them.

State of the art

1-cyclopropyl-7-([S,S])-2,8-diazadicyclo[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid hydrochloride, also known by the name moxifloxacin hydrochloride, is an antibacterial agent of formula:



which is widely used therapeutically in the treatment of infections by antibiotic-resistant bacteria.

Its preparation is reported in EP550903 and the preparation and characteristics of its monohydrate pseudopolymorph are described in US5849752. It is clear from this patent that the only known forms of moxifloxacin hydrochloride are the anhydrous form and the monohydrate, extensive identifying documentation of which is provided. In the patent, it is also written that the anhydrous form of the active ingredient is unsuitable for the preparation of pharmaceutical formulations since it absorbs water from the atmosphere. The monohydrate form, on the other hand, does

not have the disadvantage of being hygroscopic and can be prepared in the form of crystalline prisms, which confer on the powder characteristics of fluidity that are advantageous for formulation purposes, or in the form of needles which tend rather to clump together.

According to the US patent, the monohydrate in prism form can be produced by suspending moxifloxacin hydrochloride in ethanol/water mixtures containing up to 10% of water whereas, to form the monohydrate in needle form, water or any water/alcohol mixture with a water content greater than 10% may be used.

It is also mentioned in the description of the invention that, in order to produce the monohydrate form, the relative humidity value should not fall below 30% during the drying stage, since this condition would lead to the formation of the anhydrous form.

However, the examples of the preparation of moxifloxacin hydrochloride monohydrate given in US5849752 show serious limitations of industrial applicability both owing to the large volumes of solvent that are used and owing to the subsequent production technique.

In fact the method provides first of all for the anhydrous form of moxifloxacin hydrochloride to be dissolved in a large quantity of solvent and then for the solvent to be evaporated completely so that the active ingredient is recovered as the evaporation residue. However, if this evaporation to dryness is performed hot, for example, by heating to 60-70°C, it may lead to degradation of the product whereas, if it is performed spontaneously at room temperature as described in Examples 5 and 6 of the US patent, it requires very long periods of time that are not practicable industrially.

In conclusion, there is at the moment still a need to identify an industrially applicable method of producing a stable and easily formulated form of moxifloxacin

hydrochloride which does not require laborious stages for the evaporation of large volumes of solvent and which is sufficiently quick and gentle not to lead to alterations in the final product.

Description of the invention

The subjects of the present invention are therefore two novel, stable, and easily formulated crystalline forms of moxifloxacin hydrochloride, a method for the preparation thereof, and pharmaceutical formulations, which include them.

It has in fact surprisingly been found that, by means of an easily industrially applicable method, which comprises the steps of:

- a) suspending moxifloxacin hydrochloride in a suitable solvent,
- b) heating the mixture under reflux,
- c) cooling, and
- d) isolating the product which is separated,

a novel hydrated crystalline form of moxifloxacin hydrochloride, which is stable and easy to formulate, designated as moxifloxacin hydrochloride form A is obtained.

Further, by subjecting the product resulting from the above step d) to the following additional stages characterized by

- e) reslurrying the solid in a suitable solvent, and
- f) isolating the product,

another novel form of moxifloxacin hydrochloride, named form B, stable and easy to formulate too, is prepared.

The starting moxifloxacin hydrochloride may be either in amorphous form or in any crystalline form, for example, in anhydrous or monohydrate crystalline form, as described in US5849752. Preferably, the starting moxifloxacin hydrochloride is an anhydrous form having a water content of less than 0.3%.

The solvent used in the method described above is generally an alcohol or a polyol, preferably a C₁-C₆ alcohol or polyol,

for example, methanol, ethanol, isopropanol, n-propanol, n-butanol, isobutanol, terbutanol, n-pentanol, n-hexanol, 1,2-ethandiol, 1,2-propandiol, 1,3-propandiol, methoxyethanol, methoxypropanol, etc..., most preferably ethanol or isopropanol, or mixtures thereof.

In particular, the novel crystalline forms of moxifloxacin hydrochloride can be produced, in accordance with the above-described steps, by the suspension of moxifloxacin hydrochloride in the preselected solvent, provided that the resulting mixture has an overall water content of between 2.5% and 0.01% by weight. "Overall water content" means the quantity of water resulting from the sum of the water content of the starting moxifloxacin hydrochloride and of the water contained in the solvent.

Preferably, a solvent with a water content of between 1% and 0.01%, more preferably between 0.3% and 0.01%, and even more preferably between 0.1 and 0.01% is used.

The production of these novel crystalline forms is particularly surprising in the light of the misleading teaching provided by the patent US5849752; in fact in the description thereof (col. 2, lines 62-65) it is stated that "the preferred monohydrate form in the form of prisms can be obtained by suspending the crystalline anhydrous product in ethanol/water mixtures, particularly in the said mixtures with a maximum water content of 10%", thus meaning also mixtures with 2.5%, 1% or 0.1% of water. In fact, in these conditions, it has surprisingly been found that, instead of the prism form described by the US patent, form A or, following the additional steps e) - f), form B, which are the subject of the present invention, are obtained.

In the method for the preparation of form A, the solvent is generally used in a ratio of between 50:1 and 2:1, preferably between 30:1 and 5:1, more preferably about 10:1, the ratio being expressed as ml of solvent per gram of moxifloxacin hydrochloride.

The mixture of moxifloxacin hydrochloride and solvent is kept under reflux (step a) for a variable period of time which will depend on various factors such as, for example, the type of solvent, the form of the starting product, the total quantity of water, etc., and is preferably at least 1 hour, more preferably about 4 hours.

The cooling of the mixture (step b) may be spontaneous or accelerated by appropriate means known to a person skilled in the art. The mixture may be cooled to room temperature or cooling may continue to lower temperatures; in general, it is preferred to allow the mixture to cool spontaneously until room temperature is reached.

In a particularly preferred method, cooling to room temperature takes place in about 2 hours and the mixture is allowed to rest at that temperature for a further 2 hours before the isolation is performed.

The novel crystalline forms according to the invention are isolated (step d and f) by conventional techniques, for example, by filtration, decantation or centrifuging.

The novel crystalline form A of moxifloxacin hydrochloride is characterized by the X-ray diffraction spectrum (XRD) which is shown in Figure 1 and described in Table 1, by the solid-state ^{13}C -NMR spectrum which is shown in Figure 2 and tabulated in Table 2, by the IR spectrum which is given in Figure 3, and by the DSC trace which is shown in Figure 4. The differences in comparison with the known forms can clearly be distinguished by comparing this spectral data with that of the anhydrous and monohydrate forms described in US5849752. In particular, in the XRD spectrum of the novel form, characteristic peaks situated at 7.2, 12.3, 16.6 and 21.6 are distinguished and, in the solid-state ^{13}C -NMR spectrum, characteristic peaks are shown at 169.1, 164.6, 151.8, 115.7 and 67.7, as results from the following table:

Table 1

X-ray diffraction spectrum of moxifloxacin hydrochloride form A, registered on a Philips PW3710 spectrometer (X-ray Diffractometer).

(Cu K α radiation, generator voltage 40 kV, slit divergence 1°, receiving slit 0.2 mm, scan mode step start angle 5.000, end angle 35.000, time per step 2.000s)

Angle (2 θ)	D (Å)	Rel. Intens. (I/I ₀)
5.815	15.1858	49.8
7.220	12.2335	100.0
8.575	10.3032	86.1
10.335	8.5522	87.2
12.310	7.1842	19.4
13.200	6.7018	17.0
14.085	6.2826	16.3
14.535	6.0891	11.1
14.870	5.9527	20.6
15.185	5.8299	17.6
15.675	5.6487	1.9
16.620	5.3296	18.3
17.335	5.1114	60.1
17.850	4.9650	80.9
19.315	4.5916	53.7
19.760	4.4892	19.1
20.375	4.3551	2.5
21.640	4.1033	47.6
22.295	3.9842	12.7
23.160	3.8373	4.2
23.625	3.7628	1.9
24.705	3.6007	26.9
25.115	3.5428	17.6
25.815	3.4483	15.6
26.440	3.3682	39.4
27.365	3.2564	36.3
27.970	3.1874	17.8
28.360	3.1444	14.5
29.015	3.0749	28.2
29.965	2.9795	13.9
30.545	2.9243	4.8
31.575	2.8312	5.9
32.270	2.7718	12.2
33.900	2.6421	6.4

Table 2

Solid-state ¹³C-NMR absorptions of moxifloxacin hydrochloride form A (p.p.m.). Spectrum registered on Varian 400 instrument:

175.1	169.0	166.1	151.7	150.3	143.7	140.1	137.5	135.7	134.7
117.8	115.4	107.9	106.0	104.8	67.1	63.3	59.1	55.6	52.2
50.2	46.7	40.4	35.1	22.8	20.0	18.1	12.8	9.6	

The novel crystalline form A of moxifloxacin hydrochloride is stable if left in air at room temperature for 5 days (Figure 5); in fact it can be seen from the figure that the XRD profile does not differ substantially from the reference profile of the novel form A.

Moxifloxacin hydrochloride form A has workability and fluidity characteristics, which are optimal for formulation and does not lose these properties even after compression tests.

As previously stated, Moxifloxacin hydrochloride form B may be prepared according to the following steps:

- a) suspending moxifloxacin hydrochloride in a solvent selected from alcohols and polyols or mixtures thereof, in which the resulting mixture has an overall water content of between 2.5% and 0.01% by weight,
- b) heating the mixture under reflux,
- c) cooling,
- d) filtering the solid obtained,
- e) reslurrying at reflux the solid in a solvent selected from alcohols and polyols or mixtures thereof, in which the resulting mixture has an overall water content of between 2.5% and 0.01% by weight and
- f) isolating the product.

In the method above described, the solvent in both the steps a) and e) is generally used in a ratio of between 50:1 and 2:1, preferably between 30:1 and 5:1, more preferably about 10:1, the ratio being expressed as ml of solvent per gram of moxifloxacin hydrochloride.

The mixture of moxifloxacin hydrochloride and solvent is kept under reflux for a variable period of time which will depend on various factors such as, for example, the type of

solvent, the form of the starting product, the total quantity of water, etc., and is preferably at least 1 hour, more preferably about 4 hours.

The cooling of the mixture (step c) may be spontaneous or accelerated by appropriate means known to a person skilled in the art. The mixture may be cooled to room temperature or cooling may continue to lower temperatures; in general, it is preferred to allow the mixture to cool spontaneously until room temperature is reached.

In a particularly preferred method, cooling to room temperature takes place in about 2 hours and the mixture is allowed to rest at that temperature for a further 2 hours before the isolation (step d) is performed.

The product obtained is then filtered and charged again as wet in a reactor where a reslurry at reflux in one of the solvents as defined above is performed (step e), for a period of time ranging generally from 1 to 4 hours, preferably for about 2 hours. After cooling, the crystalline material is isolated (step f), generally by filtration, and dried under vacuum, preferably at 40°C for 12 hours, thus obtaining moxifloxacin hydrochloride form B.

The novel crystalline form B of moxifloxacin hydrochloride is characterized by the X-ray diffraction spectrum (XRD) which is shown in Figure 6 and described in Table 3, by the IR spectrum which is given in Figure 7, and by the DSC trace which is shown in Figure 8. The differences in comparison with the known forms can clearly be distinguished by comparing this spectral data with that of the anhydrous and monohydrate forms described in US5849752. In particular, in the XRD spectrum of the novel form B, characteristic peaks situated at 7.2, 8.8, 10.5 and 14.7 are distinguished.

Table 3

X-ray diffraction spectrum of moxifloxacin hydrochloride form B, registered on a Philips PW3710 spectrometer (X-ray Diffractometer).

(Cu K α radiation, generator voltage 40 kV, slit divergence 1°, receiving slit 0.2 mm, scan mode step start angle 5.000, end angle 35.000, time per step 2.000s)

Angle (2 θ)	D (Å)	Rel. Intens. (I/I ₀)
5.700	15.4919	24.0
7.200	12.2675	100.0
8.470	10.4307	18.9
8.820	10.0176	91.6
10.505	8.4142	44.0
11.405	7.7522	14.6
12.220	7.2369	5.9
13.200	6.7018	16.2
13.925	6.3544	18.1
14.415	6.1395	26.6
14.740	6.0049	49.9
15.395	5.7508	4.9
16.600	5.3360	20.7
17.180	5.1571	13.7
17.705	5.0034	68.7
18.710	4.7387	13.7
19.105	4.6416	26.2
19.865	4.4657	11.8
20.155	4.4021	7.6
21.055	4.2159	2.4
21.545	4.1211	16.9
22.155	4.0090	17.3
22.690	3.9157	11.8
22.905	3.8794	10.5
24.610	3.6144	18.7
24.955	3.5652	10.0
25.385	3.5058	7.0
25.815	3.4483	14.5
26.195	3.3992	16.3
26.605	3.3477	18.4
26.960	3.3044	28.7
27.265	3.2681	37.0
28.045	3.1790	9.0
28.730	3.1047	22.2
29.110	3.0651	8.5
29.745	3.0011	9.6
30.170	2.9598	6.2
31.440	2.8430	4.1
31.795	2.8121	1.9
32.145	2.7823	3.1
32.410	2.7601	2.5
33.385	2.6817	1.8

The following preparation examples are now given to illustrate some of the methods that can be used to obtain the novel crystalline forms of moxifloxacin hydrochloride but they are not intended to limit the invention in any way.

EXAMPLE 1

907.4 g of moxifloxacin hydrochloride monohydrate and 9070 ml of absolute ethanol (K.F. < 0.1%) were loaded into a 10 liter jacketed reactor and equipped with a mechanical stirrer, reflux condenser, and thermometer. The suspension was brought to reflux with stirring and was kept in those conditions for 4 hours. The temperature was then reduced to 20°C and the solid was filtered out and washed with 900 ml of absolute ethanol. The filtered solid was then discharged and dried under vacuum (30 mmHg) at 40°C for 18 hours to give moxifloxacin hydrochloride form A having a water content of about 1% (K.F.).

EXAMPLE 2

10 g of anhydrous moxifloxacin hydrochloride and 200 ml of ethanol with 0.3% K.F. were loaded into a 250 ml flask. The mixture was brought to reflux and kept in those conditions for 4 hours, after which it was cooled to room temperature. The solid product was filtered out and washed with 30 ml of absolute ethanol. The solid was dried under vacuum (30 mmHg) at 40°C for 16 hours to give 8.5 g of moxifloxacin hydrochloride form A.

EXAMPLE 3

20 g of anhydrous moxifloxacin hydrochloride and 250 ml of isopropanol with 0.2% K.F. were loaded into a 500 ml flask. The mixture was brought to reflux and was kept in those conditions for 4 hours, after which it was cooled to room temperature. The solid product was filtered out and washed with 50 ml of isopropanol. The solid was dried under vacuum (30 mmHg) at 40°C for 16 hours, to give 8.0 g of moxifloxacin hydrochloride form A.

EXAMPLE 4

10 g of anhydrous moxifloxacin hydrochloride and 200 ml of isobutanol with 0.3% K.F. were loaded into a 250 ml flask. The mixture was brought to reflux and was kept in those conditions for 4 hours, after which it was cooled to room temperature. The solid product was filtered out and washed with 30 ml of absolute ethanol. The solid was dried under vacuum (30 mmHg) at 40°C for 16 hours to give 7.8 g of moxifloxacin hydrochloride form A.

EXAMPLE 5

10 g of moxifloxacin hydrochloride monohydrate and 200 ml of 1,2-propandiol with 0.1% K.F. were loaded into a 250 ml flask. The mixture was brought to reflux and was kept in those conditions for 4 hours, after which it was cooled to room temperature. The solid product was filtered out and washed with 30 ml of absolute ethanol. The solid was dried under vacuum (30 mmHg) at 40°C for 16 hours to give 8.2 g of moxifloxacin hydrochloride form A.

EXAMPLE 6

200 mg of moxifloxacin hydrochloride form A, 200 mg of Avicel Ph 112, and 5 mg of magnesium stearate were introduced into a mortar.

The powder was mixed and transferred into a Graseby Specac press and compressed by the application of a compression force of 5 tons. The procedure described was repeated a further 10 times, producing 10 identical tablets.

EXAMPLE 7

10 g of anhydrous moxifloxacin hydrochloride and 200 ml of ethanol with 0.3% K.F. were loaded into a 250 ml flask. The mixture was brought to reflux and kept in those conditions for 4 hours, after which it was cooled to room temperature. The solid product was filtered out and washed with 30 ml of absolute ethanol. The solid was recharged in a 250 ml flask, 200 ml of absolute ethanol with 0.1% K. F. were added and the mixture was brought to reflux and maintained in these

conditions for 1 hour. Then the temperature was lowered to 25°C and the crystalline solid was filtered and washed with absolute ethanol. After drying under vacuum (30 mmHg) at 40°C for 16 hours 8.0 g of moxifloxacin hydrochloride form B were obtained.

EXAMPLE 8

20 g of moxifloxacin hydrochloride monohydrate and 250 ml of isopropanol with 0.2% K.F. were loaded into a 500 ml flask. The mixture was brought to reflux and was kept in those conditions for 4 hours, after which it was cooled to room temperature. The solid product was filtered and washed with 50 ml of isopropanol. The solid was recharged in a 250 ml flask, 200 ml of isopropanol with 0.1% K. F. were added and the mixture was brought to reflux and maintained in these conditions for 1 hour. Then the temperature was lowered to 25°C and the crystalline solid was filtered and washed with isopropanol. After drying under vacuum (30 mmHg) at 40°C for 16 hours 17.2 g of moxifloxacin hydrochloride form B were obtained.

CLAIMS

1. Moxifloxacin hydrochloride form A, characterized by an X-ray diffraction spectrum having the following principal peaks:

Angle (2 θ)	D (Å)	Rel. Intens. (I/I ₀)
5.815	15.1858	49.8
7.220	12.2335	100.0
8.575	10.3032	86.1
10.335	8.5522	87.2
12.310	7.1842	19.4
13.200	6.7018	17.0
14.085	6.2826	16.3
14.535	6.0891	11.1
14.870	5.9527	20.6
15.185	5.8299	17.6
15.675	5.6487	1.9
16.620	5.3296	18.3
17.335	5.1114	60.1
17.850	4.9650	80.9
19.315	4.5916	53.7
19.760	4.4892	19.1
20.375	4.3651	2.5
21.640	4.1033	47.6
22.295	3.9842	12.7
23.160	3.8373	4.2
23.625	3.7628	1.9
24.705	3.6007	26.9
25.115	3.5428	17.6
25.815	3.4483	15.6
26.440	3.3682	39.4
27.365	3.2564	36.3
27.970	3.1874	17.8
28.360	3.1444	14.5
29.015	3.0749	28.2
29.965	2.9795	13.9
30.545	2.9243	4.8
31.575	2.8312	5.9
32.270	2.7718	12.2
33.900	2.6421	6.4

2. Moxifloxacin hydrochloride form A, characterized by an X-ray diffraction spectrum as shown in Figure 1.
3. Moxifloxacin hydrochloride form A, characterized by a solid-state ¹³C-NMR spectrum as shown in Figure 2.
4. Moxifloxacin hydrochloride form A, characterized by an IR spectrum as shown in Figure 3.
5. Moxifloxacin hydrochloride form A, characterized by a DSC graph as shown in Figure 4.

6. A method for the preparation of moxifloxacin hydrochloride form, A which comprises the steps of:

- a) suspending moxifloxacin hydrochloride in a solvent selected from alcohols and polyols or mixtures thereof, in which the resulting mixture has an overall water content of between 2.5% and 0.01% by weight,
- b) heating the mixture under reflux,
- c) cooling, and
- d) isolating the product.

7. A method according to Claim 6 in which the moxifloxacin hydrochloride in step a) is in anhydrous or monohydrate crystalline form.

8. A method according to Claim 7 in which the moxifloxacin hydrochloride is in an anhydrous form having a water content of less than 0.3%.

9. A method according to Claim 6 in which the solvent is a C₁-C₆ alcohol or polyol, preferably ethanol or isopropanol.

10. A method according to Claim 6 in which the solvent has a water content of between 1% and 0.01%, preferably between 0.3% and 0.01%, more preferably between 0.1% and 0.01%.

11. A method according to Claim 6 in which the mixture is cooled to room temperature.

12. A method according to Claim 6 in which the solvent is used in a ratio of between 50:1 and 2:1, preferably between 30:1 and 5:1, more preferably about 10:1, the ratio being expressed as ml of solvent per gram of moxifloxacin hydrochloride.

13. A method according to Claim 6 in which the mixture is heated under reflux for at least 1 hour, preferably for about 4 hours.

14. A method for treating bacterial infections which comprises administering moxifloxacin hydrochloride form A according to Claims 1 to 5 to a patient in need of such a treatment.

15. Pharmaceutical compositions comprising moxifloxacin hydrochloride form A according to Claims 1 to 5 and at least one pharmaceutically acceptable excipient.

16. Moxifloxacin hydrochloride form B, characterized by an X-ray diffraction spectrum having the following principal peaks:

Angle (2 θ)	D (Å)	Rel. Intens. (I/I ₀)
5.700	15.4919	24.0
7.200	12.2675	100.0
8.470	10.4307	18.9
8.820	10.0176	91.6
10.505	8.4142	44.0
11.405	7.7522	14.6
12.220	7.2369	5.9
13.200	6.7018	16.2
13.925	6.3544	18.1
14.415	6.1395	26.6
14.740	6.0049	49.9
15.395	5.7508	4.9
16.600	5.3360	20.7
17.180	5.1571	13.7
17.705	5.0054	68.7
18.710	4.7387	13.7
19.105	4.6416	26.2
19.865	4.4657	11.8
20.155	4.4021	7.6
21.055	4.2159	2.4
21.545	4.1211	16.9
22.155	4.0090	17.3
22.690	3.9157	11.8
22.905	3.8794	10.5
24.610	3.6144	18.7
24.955	3.5652	10.0
25.385	3.5058	7.0
25.815	3.4483	14.5
26.195	3.3992	16.3
26.605	3.3477	18.4
26.960	3.3044	28.7
27.265	3.2681	37.0
28.045	3.1790	9.0
28.730	3.1047	22.2
29.110	3.0651	8.5
29.745	3.0011	9.6
30.170	2.9598	6.2
31.440	2.8430	4.1
31.795	2.8121	1.9
32.145	2.7823	3.1
32.410	2.7601	2.5
33.385	2.6817	1.8

17. Moxifloxacin hydrochloride form B, characterized by an X-ray diffraction spectrum as shown in Figure 6.

18. Moxifloxacin hydrochloride form B, characterized by an IR spectrum as shown in Figure 7.
19. Moxifloxacin hydrochloride form B, characterized by a DSC graph as shown in Figure 8.
20. A method for the preparation of moxifloxacin hydrochloride form B, which comprises the steps the steps of:
 - a) suspending moxifloxacin hydrochloride in a solvent selected from alcohols and polyols or mixtures thereof, in which the resulting mixture has an overall water content of between 2.5% and 0.01% by weight,
 - b) heating the mixture under reflux,
 - c) cooling,
 - d) isolating the product,
 - e) reslurrying at reflux the solid in a solvent selected from alcohols and polyols or mixtures thereof, in which the resulting mixture has an overall water content of between 2.5% and 0.01% by weight and
 - f) isolating the product.
21. A method according to Claim 20 in which the moxifloxacin hydrochloride in step a) is in anhydrous or monohydrate crystalline form.
22. A method according to Claim 21 in which the moxifloxacin hydrochloride is in an anhydrous form having a water content of less than 0.3%.
23. A method according to Claim 20 in which the solvent of steps a) and e) is a C₁-C₆ alcohol or polyol, preferably ethanol or isopropanol.
24. A method according to Claim 20 in which the solvent of steps a) and e) has a water content of between 1% and 0.01%, preferably between 0.3% and 0.01%, more preferably between 0.1% and 0.01%.
25. A method according to Claim 20 in which the mixture is cooled to room temperature.

26. A method according to Claim 20 in which the solvent is used in a ratio of between 50:1 and 2:1, preferably between 30:1 and 5:1, more preferably about 10:1, the ratio being expressed as ml of solvent per gram of moxifloxacin hydrochloride.
27. A method according to Claim 20 in which step e) is performed by heating the mixture under reflux for 1 to 4 hours, preferably for about 2 hours.
28. A method for treating bacterial infections, which comprises administering moxifloxacin hydrochloride form B according to Claims 16 to 19 to a patient in need of such a treatment.
29. Pharmaceutical compositions comprising moxifloxacin hydrochloride form B according to Claims 16 to 19 and at least one pharmaceutically acceptable excipient.

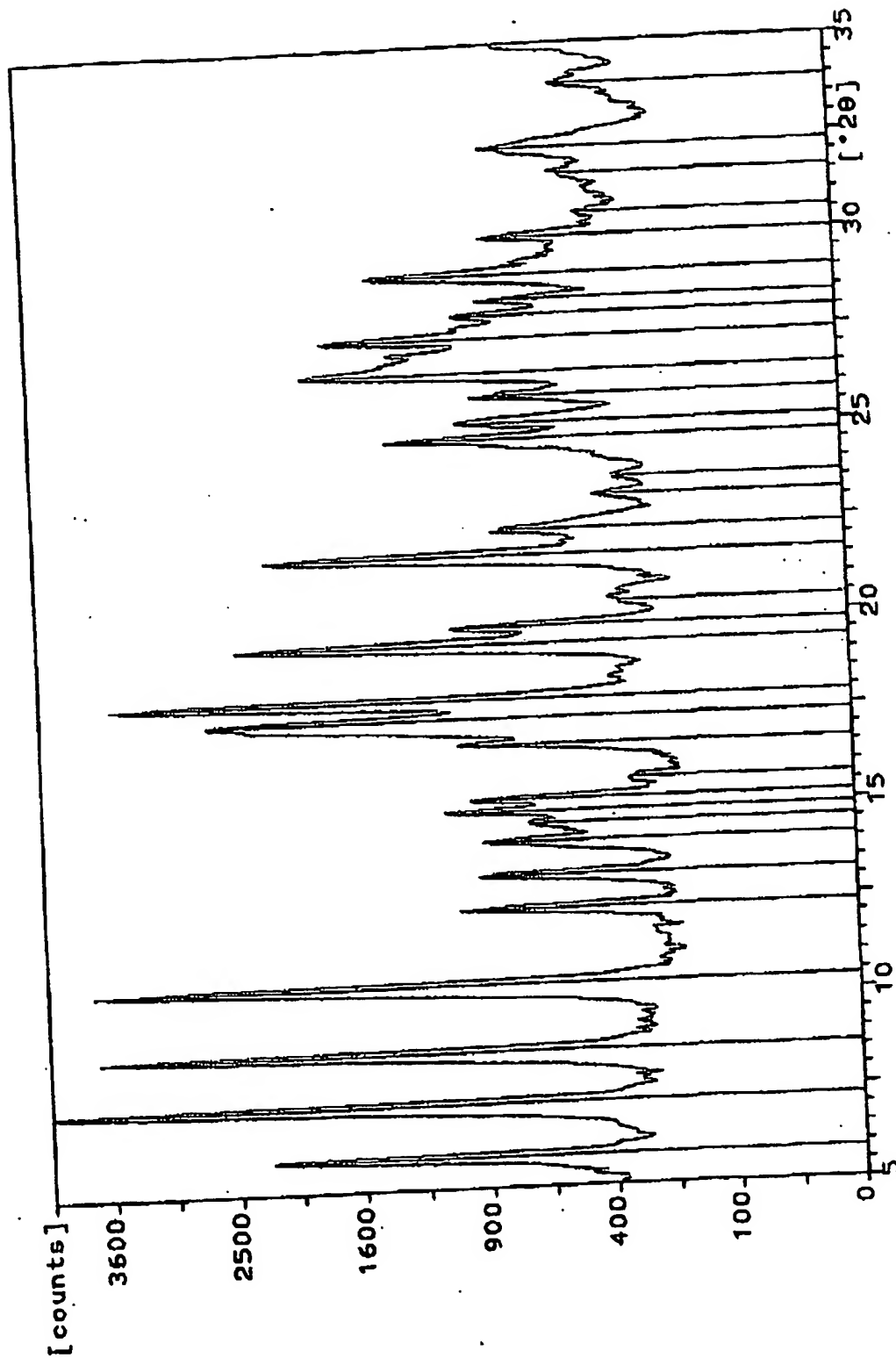


FIGURE 1

BEST AVAILABLE COPY

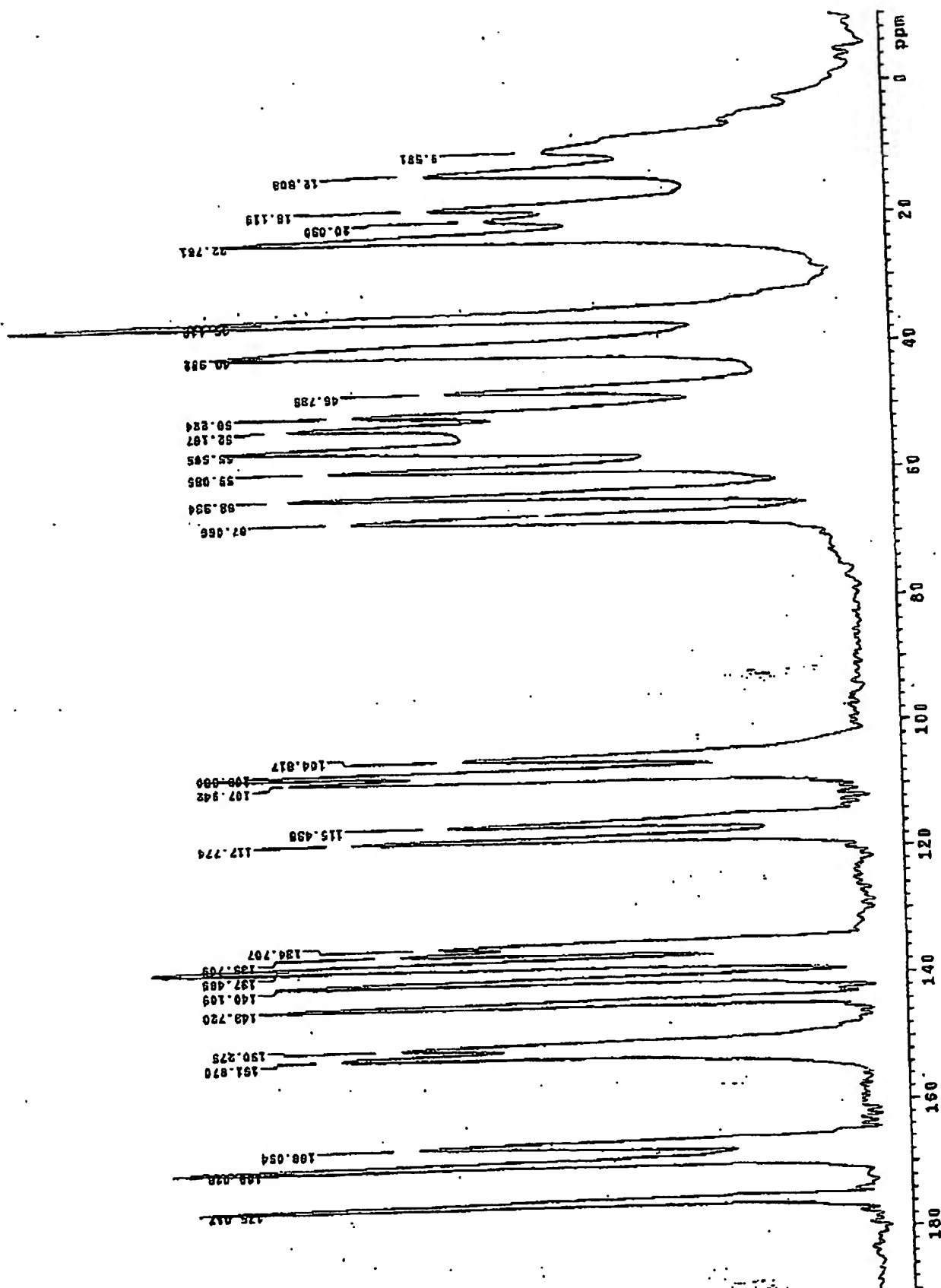


FIGURE 2

BEST AVAILABLE COPY

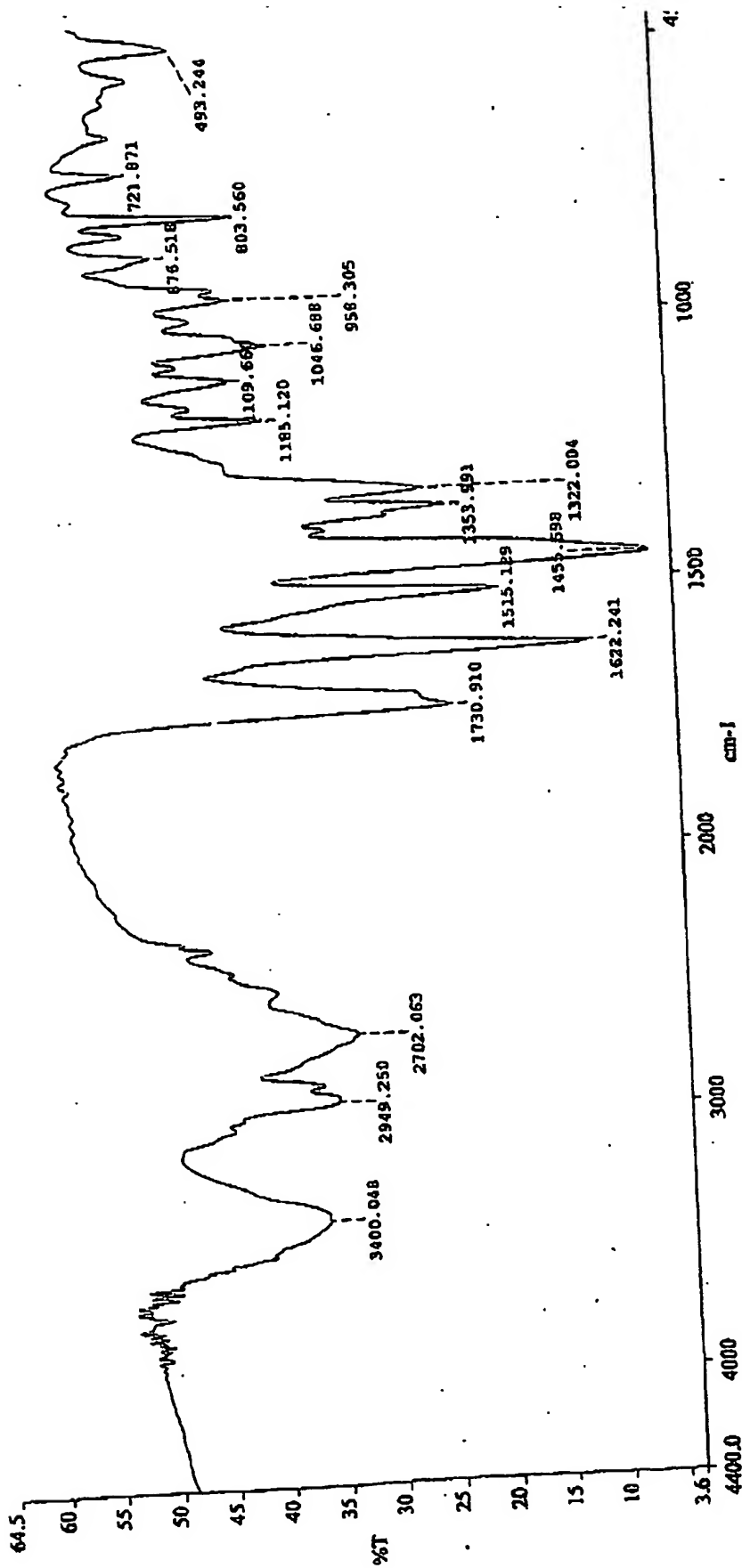


FIGURE 3

BEST AVAILABLE COPY
BEST AVAILABLE COPY

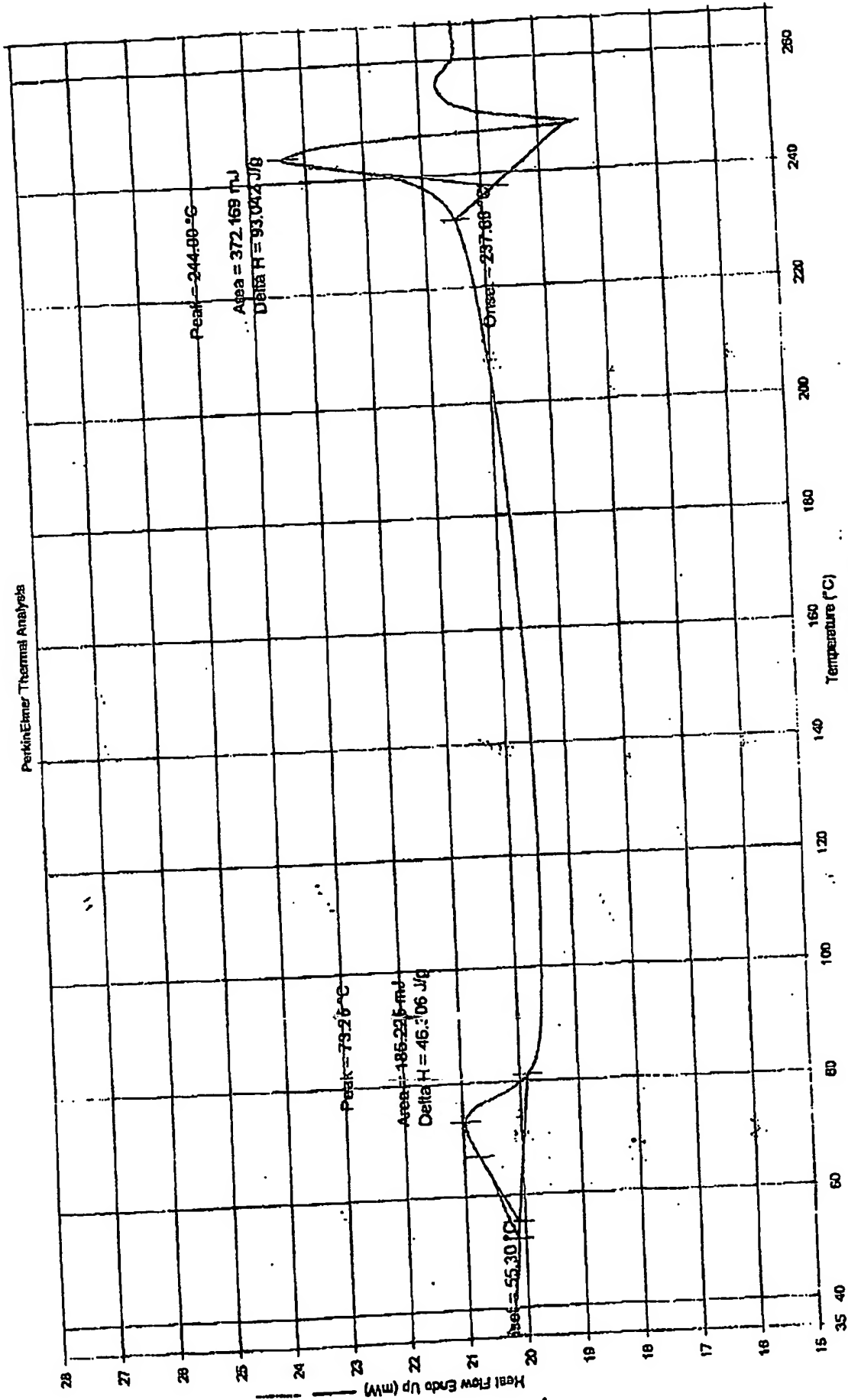


FIGURE 4

BEST AVAILABLE COPY

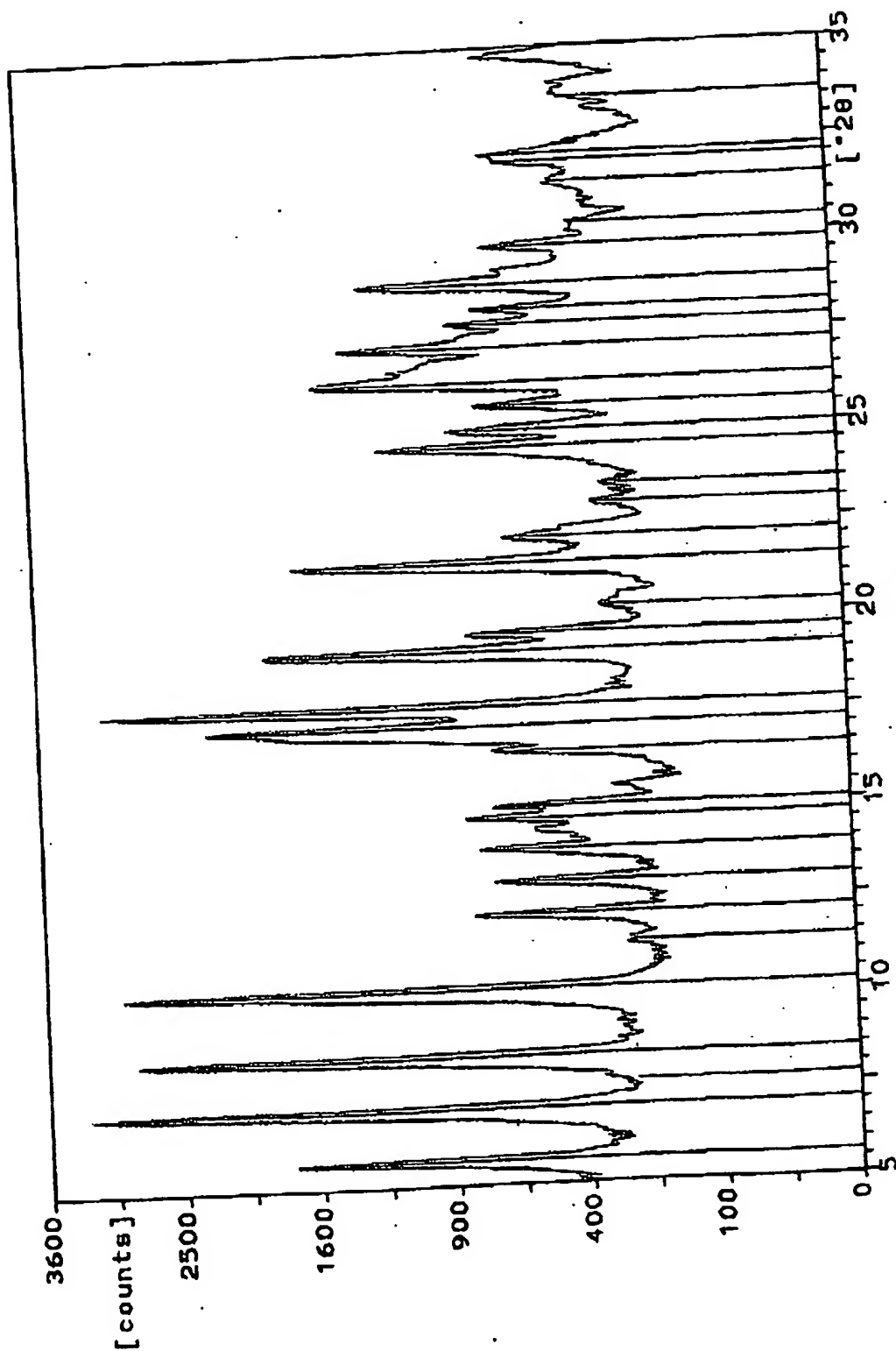


FIGURE 5

BEST AVAILABLE COPY

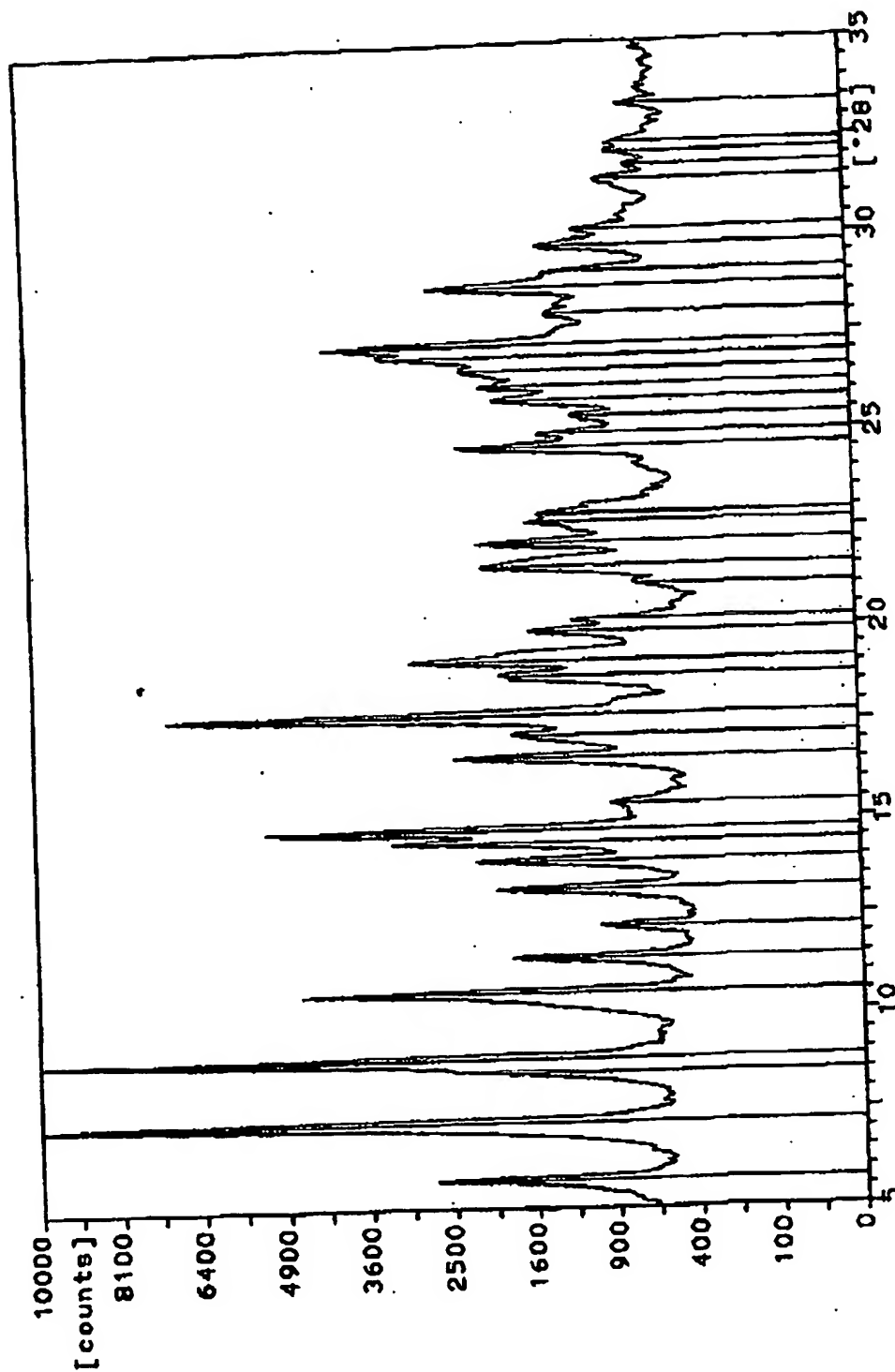


FIGURE 6

BEST AVAILABLE COPY

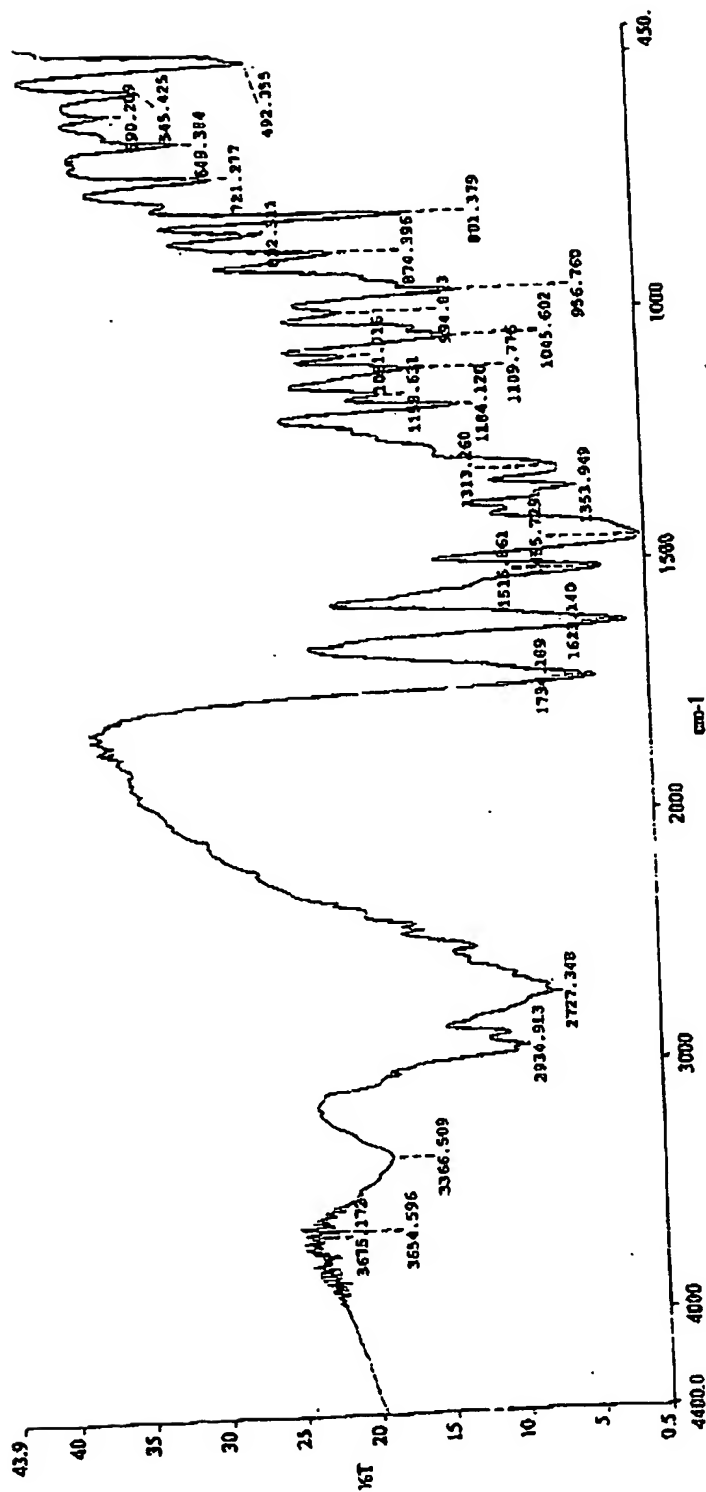


FIGURE 7

BEST AVAILABLE COPY

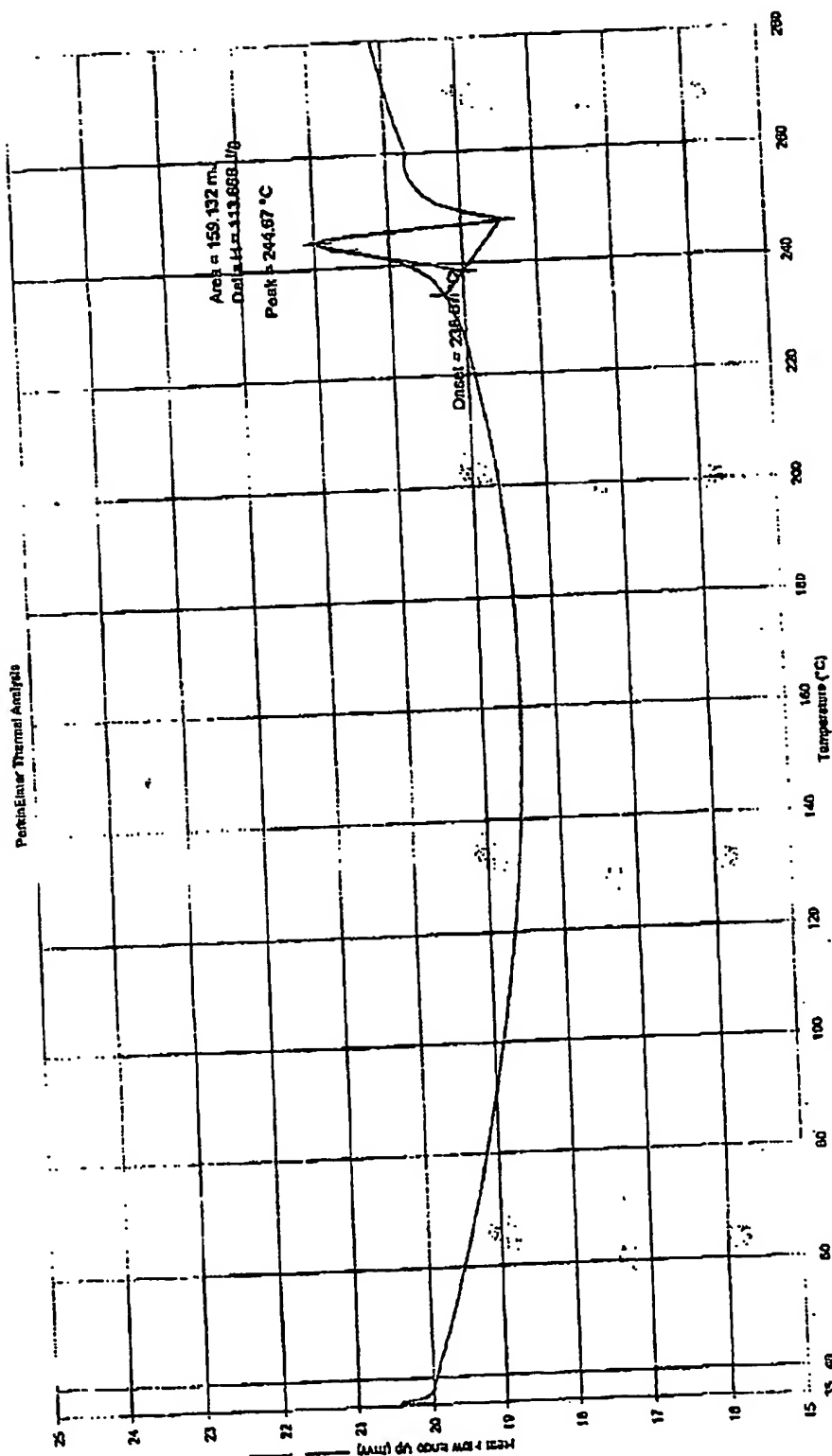


FIGURE 8

BEST AVAILABLE COPY

Application Data Sheet

Application Information

Application Type::	Provisional
Subject Matter::	Utility
Suggested Group Art Unit::	N/A
CD-ROM or CD-R?::	None
Sequence submission?::	None
Computer Readable Form (CRF)?::	No
Title::	NOVEL POLYMORPHS OF 1-CYCLOPROPYL-7-([S,S])-2,8-DIAZADICYCLO[4.3.0]NON-8-YL)-6-FLUORO-1,4-DIHYDRO-8-METHOXY-4-OXO-3-QUINOLINE CARBOXYLIC ACID HYDROCHLORIDE AND METHODS FOR THE PREPARATION THEREOF
Attorney Docket Number::	02901/0200758-US0
Request for Early Publication?::	No
Request for Non-Publication?::	No
Small Entity?::	No
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	Italy
Status::	Full Capacity
Given Name::	Stefano
Family Name::	Turchetta
City of Residence::	Roma
Country of Residence::	Italy
Street of mailing address::	Piazza Vinci 13

City of mailing address:: Roma
Country of mailing address:: Italy
Postal or Zip Code of mailing address:: 00139

Applicant Authority Type:: Inventor
Primary Citizenship Country:: Italy
Status:: Full Capacity
Given Name:: Pietro
Family Name:: Massardo
City of Residence:: Roma
Country of Residence:: Italy
Street of mailing address:: Via Beccari 24
City of mailing address:: Roma
Country of mailing address:: Italy
Postal or Zip Code of mailing address:: 00154

Applicant Authority Type:: Inventor
Primary Citizenship Country:: Italy
Status:: Full Capacity
Given Name:: Valentina
Family Name:: Aromatario
City of Residence:: Roma
Country of Residence:: Italy
Street of mailing address:: ~~Via Salvatore~~ Talamo 20
City of mailing address:: Roma
Country of mailing address:: Italy
Postal or Zip Code of mailing address:: 00177

Correspondence Information

Correspondence Customer Number:: 07278

Representative Information

Representative Customer Number:: 07278

Assignee Information

Assignee name:: CHEMI SPA

Street of mailing address:: Via dei Lavoratori 54,
Cinisello Balsamo

City of mailing address:: Milano

Country of mailing address:: Italy

Postal or Zip Code of mailing address:: 20092

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP04/052699

International filing date: 28 October 2004 (28.10.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/532,779
Filing date: 24 December 2003 (24.12.2003)

Date of receipt at the International Bureau: 28 December 2004 (28.12.2004)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse